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(54) Title: THE USE OF A GLUCOCORTICOID RECEPTOR II ANTAGONIST TO TREAT DEPRESSION IN PATIENTS TAKING IL-2

(57) Abstract: The invention pertains to the discovery that type II glucocorticoid receptor antagonists can be used in methods for reversing or inhibiting the symptoms of depression in patients receiving interleukin-2 treatment.



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THE USE OF A GLUCOCORTICOID RECEPTOR II ANTAGONIST TO TREAT DEPRESSION IN PATIENTS TAKING IL-2

CROSS-REFERENCES TO RELATED APPLICATIONS

- 5 [0001] This application claims benefit of U.S. Provisional Application No. 60/797,265, filed May 2, 2006, which is herein incorporated by reference in its entirety.

FIELD OF INVENTION

[0002] This invention relates to the use of glucocorticoid receptor antagonists as a method for ameliorating the symptoms of depression in a patient taking interleukin-2 (IL-2).

BACKGROUND OF THE INVENTION

10

[0003] Cytokines are small protein molecules that are actively secreted by immune cells and other cell types. Cytokines function to orchestrate immune system responses and coordinate those responses with other physiological systems in the body. Their action is often local, but can effect the whole body, including the nervous system. Common examples
15 of cytokines include interferon- α (IFN α), IFN β , IFN γ , interleukin-1 (IL-1), IL-2, IL-6, IL-10, granulocyte macrophage-colony stimulating factor (GM-CSF), and tumor necrosis factor- α (TNF- α).

[0004] Cytokines have been shown to be effective in the treatment of a variety of medical conditions, such as hepatitis C, multiple sclerosis, certain infections, leukemia, Kaposi's
20 sarcoma, melanoma, myeloma, renal carcinoma, and other forms of cancer. The most commonly used cytokines for medical therapy include IL-2, IFN α , β , and γ . See, *e.g.*, Dunn *et al.*, *Neurosci. and Behav. Rev.* **29**:891-909 (2005).

[0005] IL-2 is a potent immune stimulator activating diverse cells in the immune system, including T cells, B cells and monocytes. IL-2 is a potent and critical stimulator for T cell
25 proliferation. IL-2 stimulates the cytolytic activity of NK cells and stimulates the secretion of additional cytokines, including IFN γ , GM-CSF, and TNF- α . IL-2 also enhances the proliferation and antibody secretion by normal B-cells, and stimulates the cytotoxic activities of activated macrophages, promoting the further secretion of TNF- α , IL-1 and IL-6. It was

by virtue of these activities that IL-2 was tested and approved for the treatment of cancer. IL-2 has been used as a therapeutic agent for the treatment of various forms of cancer since 1981, and has been shown to be effective for the treatment of renal cell carcinoma, and metastatic melanoma in some patients (see, *e.g.*, Wichers and Maes, *Int. J.*

- 5 *Neuropsychopharm.* 5:375-388 (2002)). Each of the cytokines commonly used for medical treatment, however, is reported to produce side-effects such as asthenia, myalgia, confusion, and influenza-like symptoms. Depression is most commonly associated with IFN α and IL-2, and occasionally with IFN β (see Dunn *et al.*, *supra*).

[0006] Depression may be caused by cytokine secretion associated with an activation of the
10 immune system. The incidence of immune abnormalities is higher in depressed patients as compared to the general population, and depression is a common side-effect of cytokine therapy (Dunn *et al.*, *supra*).

[0007] Clinical observations have indicated that patients being treated with interferons or IL-2 display influenza like symptoms and nonspecific neuropsychiatric symptoms, some of
15 which are characteristic of depression. In animal studies, immune activation and administration of the bacterial endotoxin lipopolysaccharide (LPS) or IL-1 can induce a behavioral pattern resembling that commonly observed in sick animals, including humans. This behavioral pattern is known as sickness behavior, and shares many of the symptoms of depression and anxiety that may be attenuated by antidepressant agents (See, *e.g.*, Anisman
20 and Merali, *Annal. of Med.* 35:2-11 (2003)).

[0008] Furthermore, IL-2 may induce anhedonic effects, a prominent feature of depression. Depressive illness is accompanied by signs of immune activation and elevated cytokine production or elevated levels of circulating cytokines, particularly IL-2, IL-1, IL-6, TNF- α , and IFN- γ . In addition, immunotherapy with IL-2 or IFN- α may result in a depression-like
25 state that may be attenuated by treatment with an antidepressant.

[0009] Cortisol acts by binding to an intracellular glucocorticoid receptor (GR). In humans, glucocorticoid receptors are present in two forms: a ligand-binding GR-alpha of 777 amino acids; and a GR-beta isoform that differs in only the last fifteen amino acids. The two types of GR have high affinity for their specific ligands, and are considered to function
30 through the same signal transduction pathways.

[0010] Hypercortisolism has been observed in depressed patients. Glucocorticoids (GC) are reported to suppress long-term potentiation, inhibit neurogenesis, and stimulate excitatory amino acid neurotransmitter release, which causes hippocampal atrophy and memory impairment. (See, *e.g.*, Song, *Brain Behav. Immun.* 16:557-568 (2002)). Similar effects have been reported with pro-inflammatory cytokines, such as IL-1 β (Song, 2002, *supra*). It is also well established that pro-inflammatory cytokines directly stimulate the hypothalamic-pituitary adrenal (HPA) axis to secrete cortisol, significantly increasing GC secretion (See, *e.g.*, Song, 2002, *supra*; Connor *et al.*, *Neuroscience* 84:923-933 (1998)). In fact, studies in rats suggest that the IL-1 induced memory deficits are related to the effect of IL-1 on CRF and GCs. In these studies, rats that were given an intracerebroventricular (i.c.v.) injection of the GC antagonist RU486 immediately prior to receiving administration of IL-1 showed significant reduction in learning and memory impairments typically associated with IL-1 administration. Furthermore, rats that did not recover from the deleterious effects of IL-1, even after several days, showed complete recovery after one or two treatments with RU486. These studies strongly support the notion that GCs mediate the effect of IL-1 on learning and memory (Song, 2002, *supra*).

[0011] The biological effects of cortisol, including pathologies or dysfunctions caused by hypercortisolemia, can be modulated and controlled at the GR level using receptor antagonists. Several different classes of agents are able to act as GR antagonists, *i.e.*, to block the physiologic effects of GR-agonist binding (the natural agonist is cortisol). These antagonists include compositions that, by binding to GR, block the ability of an agonist to effectively bind to and/or activate the GR. One family of known GR antagonists, mifepristone and related compounds, are effective and potent anti-glucocorticoid agents in humans (Bertagna, *J. Clin. Endocrinol. Metab.* 59:25, 1984). Mifepristone binds to the GR with high affinity, with a K of dissociation $< 10^{-9}$ M (Cadepond, *Annu. Rev. Med.* 48:129, 1997). Thus, in one embodiment of the invention, mifepristone and related compounds are used to ameliorate the symptoms of depression associated with IL-2 therapy.

[0012] Previous studies have suggested that hypercortisolemia is a common feature of major depression (Murphy *J. Steroid Biochem Mol. Biol.* 38:537-558 (1991)). Furthermore, major depression that is resistant to conventional therapy has been shown to respond to inhibitors of steroid biosynthesis (Murphy *J. Steroid Biochem Mol. Biol.* 39:239-244 (1991); U.S. Pat No 4,814,333). These studies prompted a further investigation to examine the effects of the glucocorticoid receptor antagonist RU486 as a treatment for severe major

depression of very long standing in patients who were extremely resistant to treatment (Murphy *J Psych and Neurosci.* 18(5):209-213 (1993)). This study, which purports to examine the effects of RU486 on patients with severe major depression contained four patients, only one of which completed the treatment. In addition, the study, which did not
5 contain a control group against which the results could be measured, showed no clear evidence that RU486 was effective in treating depression.

[0013] The results obtained by Murphy, et al., do however, suggest that the methods described in U.S. Pat No. 4,814,333 would not be effective in treating patients suffering from IL-2 induced depression. Furthermore, the patients treated by the methods disclosed in
10 Murphy and U.S. Pat No 4,814,333 can be distinguished from the methods described herein, in that the present methods are directed toward treatment of patients not suffering from depression and having normal cortisol levels at the time IL-2 therapy is commenced.

[0014] Symptoms of depression can be detected by various methods well established in the art, including regular physical examinations and neuropsychiatric examinations (e.g.
15 Hamilton Rating Scale). Certain laboratory tests can also facilitate the diagnosis and assessment of depression. Description of detailed diagnostic methods and criteria can be found in a number of publications in the art. One such example is *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV).

[0015] Many of the actions of cortisol in the brain are mediated by binding to the type I
20 (mineralocorticoid) receptor, which is preferentially occupied, relative to the type II (glucocorticoid) receptor, at physiological cortisol levels (Ron de Kloet, et al., *Trends in Neurosci.* 22(10):422-426 (1999)). As cortisol levels increase, more glucocorticoid receptors are occupied and activated. Because cortisol plays an essential role in metabolism, inhibition of all cortisol-mediated activities, however, would be fatal. Therefore, antagonists that
25 specifically prevent type II glucocorticoid receptor functions but do not antagonize type I mineralocorticoid receptor functions are of particular use in this invention. Mifepristone and similar antagonists are examples of this category of receptor antagonists.

[0016] While there is strong evidence to suggest that cytokines such as IL-2 can contribute to depression, it is notable that neither acute nor repeated administration of IL-2 influences
30 the plasma levels of corticosterone. (See, e.g., Anisman and Merali, 2003, *supra*; Lacosta, et al., *Neuroimmunomod.* 9:1-16 (2000); Song, 2002, *supra*). Given the multitude of effects of IL-2, and the fact that IL-2 does not effect the plasma or brain levels of cortisol, it is

surprising that the symptoms of depression associated with IL-2 therapy are ameliorated by treatment with glucocorticoid receptor antagonists.

[0017] For IL-2 therapy to be maximally beneficial, the adverse side effects, especially those associated with depression, must be minimized. The present inventors have determined
5 that glucocorticoid receptor antagonists such as mifepristone are effective agents for ameliorating the symptoms of depression in patients undergoing IL-2 therapy, who are not otherwise clinically depressed and are not taking type II glucocorticoid receptor antagonists for another reason. The present invention therefore fulfills the need for an effective measure for preventing or delaying the onset of the symptoms of depression associated with IL-2
10 therapy, or for ameliorating or reversing the symptoms of depression associated with IL-2 therapy, by providing methods of administering glucocorticoid receptor antagonists to patients undergoing IL-2 therapy.

BRIEF SUMMARY OF THE INVENTION

[0018] The invention provides a method of ameliorating the symptoms of depression in a
15 patient taking IL-2 and having normal cortisol levels and not suffering from clinical depression, as diagnosed by a professional, at the time IL-2 therapy is commenced. The method comprises administration of a therapeutically effective amount of a glucocorticoid receptor antagonist to the patient, with the proviso that the patient is not otherwise suffering from a disease for which treatment using glucocorticoid receptor antagonists is indicated.

20 [0019] In one embodiment of the invention, the method of ameliorating the symptoms of depression is achieved by administering the glucocorticoid receptor antagonist to the patient undergoing IL-2 therapy.

[0020] In another embodiment of the invention, a glucocorticoid receptor antagonist is co-administered to the patient concomitantly with the IL-2 therapy.

25 [0021] In another embodiment of the invention, the glucocorticoid receptor antagonist is administered to the patient throughout the course of the IL-2 therapy.

[0022] In another embodiment of the invention, the GRA is administered to the patient taking IL-2 in conjunction with other treatment methods.

[0023] In another embodiment of the invention, the GRA is a steroid compound.

[0024] In another embodiment of the invention, the GRA has a cortisol steroid backbone with one of the following modifications or derivatives: removal of the 11- β -hydroxy group, aryl substitution of the 11- β -hydroxy group, 11- β -phenyl-aminodimethyl steroids, 17- β -side chain modifications, alpha-keto-methane-sulfonate derivatives, and androgen type steroids.

5 Examples of such compounds include dexamethasone-oxetanone, 4-pregnene-11-beta,17-alpha,21-triol-3,20-dione-21-methane-sulfonate, 16-methyl-9 alpha-fluoro-1,4-pregnadiene-11 β ,17-alpha,21-triol-3,20-dione-21-methane-sulfonate, 11- β -(4-dimethyl-aminoethoxyphenyl)-17-alpha-(propynyl-17-beta-hydroxy-4,9-estradien-3-one, and 17- β -hydroxy-11- β -(4-dimethyl-aminophenyl)17-alpha-(1-propynyl)estra-4,9-dien-3-one.

10 **[0025]** In another embodiment of the invention, the glucocorticoid receptor antagonist comprises a steroidal skeleton with at least one phenyl-containing moiety in the 11-beta position of the steroidal skeleton. The phenyl-containing moiety in the 11-beta position of the steroidal skeleton can be a dimethylaminophenyl moiety. An example of such a glucocorticoid receptor antagonist would be mifepristone, RU009 and RU044.

15 **[0026]** In another embodiment of the invention, the glucocorticoid receptor antagonist includes any steroid backbone modification which effects a biological response resulting from a GR agonist interaction. Examples of GR antagonists known in the art are discussed in more detail below, but include (6 β , 11 β , 17 β)-11-(4-dimethyl-aminophenyl)-6 methyl-4', 5' - dihydro [estra-4, 9-diene-17, 2' (3H')-furan]-3-one ("Org 31710", see Mizutani, *J Steroid*
20 *Biochem Mol Biol* 42(7):695-704, 1992), Org31806, Org34517, Org34116, RU43044, (17-beta-hydroxy-11-beta-4-/[methyl]-[1-methylehtyl]aminophenyl/-17 alpha-[prop-1-ynyl]estra-4-9-diene-3-one ("RU40555", see Kim, *J Steroid Biochem Mol Biol.* 67(3):213-22, 1998), RU28362, and ZK98299.

[0027] In another embodiment of the invention, the GRA is steroid compound which
25 effects a biological response resulting from a GR agonist interaction. Examples of compounds known in the art, and discussed in more detail below, include (6 β ,11 β ,17 β)-11-(4-(dimethyl-amino)phenyl)-6-methyl-4',5'-dihydro[estra-4,9-diene-17,2'(3H')-furan]-3-one, (11 β ,17 β)-11-(1,3-benzodioxol-5-yl)-17-hydroxy-17-(1-propynyl)e-stra-4,9-dien-3-one, (11 β ,17 α)-11-(4-acetylphenyl)-17,23-epoxy-19,24-dinorchola-4,-9,20-trien-3-one,
30 (7 β ,11 β ,17 β)-11-(4-(dimethylamino)phenyl)-7-Me-4',5'-dihydrospiro(oestra-4,9-diene-17,2'(3H)-furan)-3-one]-, (11 β , 17 α)-11,21-Bis[4-(dimethylamino)phenyl]-17-hydroxy-19-

norpregna-4,9,dien-20-yn-3-one, and (11 β ,17 α)-11-[4-(dimethylamino)phenyl]-17-hydroxy-21-[4-(methylsulfonyl)phenyl]-19-norpregna-4,9-dien-20-yn-3-one.

[0028] In yet another embodiment of the invention, the GRA is mifepristone.

[0029] In another embodiment of the invention, the GRA is a non-steroidal compound that effects a biological response resulting from a GR agonist interaction by interfering with the binding between the agonist and GR. Examples of compounds known in the art, and discussed in more detail below, include: 4b(S)-benzyl-7(S)-hydroxy-7-(1-propynyl)-4b,5,6,7,8,8a(R),9,10-octahydrophenanthrene-2-carboxylic acid (pyridine-4-ylmethyl)amide, 4b(S)-benzyl-7(S)-hydroxy-7-(3,3,3-trifluoropropyl)-4b,5,6,7,8,8a(R),9,10-octahydrophenanthrene-2-carboxylic acid (2-methylpyridin-3-ylmethyl)amide, 1-(o-chloro-alpha,alpha-diphenylbenzyl)imidazole, N(triphenylmethyl)imidazole, N-([2-fluoro-9-phenyl]fluorenyl)imidazole, N-([2-pyridyl]diphenylmethyl)imidazole, N-([4,4',4"]-trichlorotrityl)imidazole, and N((2,6 dichloro-3-methylphenyl)diphenyl)methylimidazole.

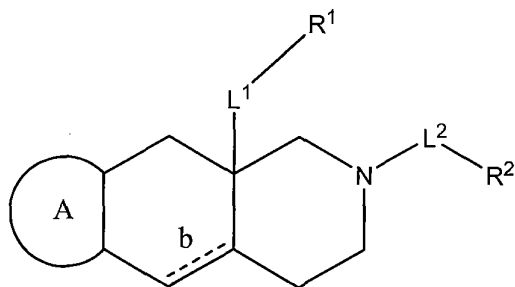
[0030] In yet another embodiment of the invention, the non-steroidal compound is derived from a chemical class known to give rise compounds that affect a biological response resulting from a GR agonist interaction. Examples of such groups from which GRA for use with the invention are discussed more fully below, but include 6-substituted-1,2-dihydro-N protected-quinolines, octahydrophenanthrenyl carbamates, oxadiazolylalkoxyoctahydrophenanthrenes, and octahydrophenanthrene hydrazines, octahydro-2-H-naphthol[1,2,-f]indole-4 carboxamide, cyclopent[f]indazole, and benz[f]indazole, 6H-dibenzo[b,d]pyran derivatives, substituted aminobenzene derivatives, triphenylmethane derivatives, diphenyl ether derivatives, and modified pyrimidine compounds. Examples of non-steroid GRA's known in the art that are suitable for use with the invention and discussed more fully below include: 1-(2-chlorotrityl)-2-methylimidazole, N-(2-chlorotrityl)-L-prolinol acetate, 1-(2-chlorotrityl)-1,2,4-triazole, and 1-(2-chlorotrityl)-3,5-dimethylpyrazole, cis-1-acetyl-4-(4-((2-(2,4-dichlorophenyl)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl)methoxy)phenyl)piperazine, N-(2[4,4',4"-trichlorotrityl]oxyethyl)morpholine, 1-(2[4,4',4"-trichlorotrityl]oxyethyl)-4(2-hydroxyethyl)piperazine dimaleate, 4-(morpholinomethyl)-A-(2-pyridyl)benzhydrol, and 1,S-bis(4,4',4"-trichlorotrityl)-1,2,4-triazole-3-thiol, 9-(3-mercapto-1,2,4 triazolyl)-9-phenyl-2,7-difluorofluorenone, 5-(5-methoxy-2-(N-methylcarbamoyl)-phenyl)dibenzosuberol, 4a(S)-

benzyl-2(R)-chloroethynyl-1,2,3,4,4a,9,10,10a(R)-octahydro-phenanthrene-2,7-diol, and 4a(S)-benzyl-2(R)-prop-1-ynyl-1,2,3,4,4a,9,10,10a(R)-octahydro-phenanthrene-2,7-diol.

[0031] In another embodiment of the invention, the glucocorticoid receptor antagonist comprises a non-steroidal compound. Examples of non-steroidal GR antagonist compounds, and modified pyrimidine compounds as disclosed in PCT US05/23675.

[0032] In other embodiments of the invention, the GRA is administered in a daily amount of between 0.5 mg and 20 mg per kg of body weight per day, preferably between about 1 mg and 10 mg per kg of body weight per day, or preferably between 1mg and 4 mg per kg of body weight per day, preferably. The invention further provides that the GRA is administered once per day and/or where administration is oral, by a transdermal application, by a nebulized suspension, by an aerosol spray, or by injection, or by an intravaginal or intrarectal route, including suppositories.

[0033] In another embodiment of the invention, the glucocorticoid receptor antagonist is an azadecalin or a fused ring azadecalin compounds known in the art, discussed in more detail below, but those compounds disclosed in U.S. Pat. App. 20040176595, azadecalin and related compounds disclosed in PCT/US05/08049 having the general formula:



(I)

[0034] In formula (I), L^1 and L^2 are members independently selected from a bond, substituted or unsubstituted alkylene, and substituted or unsubstituted heteroalkylene. The dashed line b is optionally a bond. Ring A is a member selected from substituted or unsubstituted 5 to 6 membered heterocycloalkyl, and substituted or unsubstituted heteroaryl. R^1 is a member selected from substituted or unsubstituted higher alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, and $-OR^{1A}$. R^{1A} is a member selected from substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted

heteroaryl; and R^2 is a member selected from substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, - $S(O_2)R^{2A}$, - $S(O_2)NR^{2B}R^{2C}$, = NOR^{2D} . R^{2A} , R^{2B} , R^{2C} , and R^{2D} are members independently
5 selected from substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl.

[0035] In other embodiments of the invention, the glucocorticoid receptor antagonist is administered in a daily amount of between about 0.5 to about 20 mg per kilogram of body
10 weight per day, preferably between about 1 to about 10 mg per kilogram of body weight per day or preferably between about 1 to about 4 mg per kilogram of body weight per day. The invention further provides for methods where the GRA is administered once a day and/or where the GRA is administered by mouth (orally), by transdermal application, by a nebulized suspension, by an aerosol spray, by injection, or by an intraocular, intravaginal intrarectal
15 route, including suppositories.

[0036] A further understanding of the nature and advantages of the present invention is realized by reference to the remaining portions of the specification and claims.

[0037] All publications, patents, and patent applications cited herein are hereby expressly incorporated by reference for all purposes.

20 DETAILED DESCRIPTION OF THE INVENTION

[0038] This invention pertains to the surprising discovery that agents capable of inhibiting glucocorticoid-induced biological responses are effective for ameliorating the symptoms of depression in patients taking IL-2. In patients who are to begin, or are currently undergoing, or have completed IL-2 therapy, the methods of the invention can ameliorate the symptoms
25 of depression associated with IL-2 therapy. The methods of the invention are effective in ameliorating the symptoms of depression associated with IL-2 therapy in a patient afflicted with either normal, increased, or decreased levels of cortisol or other glucocorticoids, natural or synthetic.

[0039] As the methods of the invention include the use of any means to interfere with the
30 binding between an agonist and GR and to therefore inhibit the downstream biological effects, illustrative compounds and compositions that can be used to treat depression induced

by IL-2 treatment are also set forth. Routine procedures that can be used to identify further compounds and compositions able to block the biological response caused by a GR-agonist interaction for use in practicing the methods of the invention are also described. As the invention provides for administering these compounds and compositions as pharmaceuticals, routine means to determine GR antagonist drug regimens and formulations to practice the methods of the invention are set forth below.

I. DEFINITIONS

[0040] As used herein, the term "ameliorating the symptoms of depression" refers to: (1) preventing or delaying the onset of symptoms of depression associated with IL-2 administration in a patient being treated with IL-2, but does not yet experience or exhibit symptoms of depression (prophylactic treatment), or (2) inhibiting the symptoms of depression and any further development of the symptoms to provide relief from the symptoms or side effects of depression (including palliative treatment), or (3) reversing the symptoms of depression (causing regression of the symptoms of depression). Amelioration of the symptoms of depression can be based on objective or subjective parameters, including the results of a physical examination, a neuropsychiatric examination, and/or a psychiatric evaluation.

[0041] The term "Interleukin-2" is used synonymously with "IL-2." As used herein, IL-2 refers to a protein whether native, recombinant, or made in a laboratory (e.g., aldesleukin), having the 133 normally occurring amino acid sequence of a native human IL-2 (less the signal peptide, consisting of an additional 20 N-terminal amino acids), whose amino acid sequence is described in Fujita, et al., *PNAS USA*, 80:7437-7441 (1983), with or without an additional N-terminal methionine which is necessarily included when the protein is expressed as an intracellular fraction in *E. coli*, or biologically active fragments, or variants thereof.

[0042] IL-2 may be used to treat cancer (e.g. metastatic melanoma or renal carcinoma), or other diseases known in the art. Properties displayed by IL-2 include but are not limited to: enhancing the ability of the body's immune system to fight disease; to kill tumor cells; to stimulate the cytolytic activity of NK cells; and to stimulate the secretion of additional cytokines including IFN γ , GM-CSF, and TNF α , IL-1 and IL-6.

[0043] IL-2 can also be defined by its ability to be bound by antibodies manufactured to recognize IL-2. Examples of commercially available antibodies that bind human IL-2

include: 4IL34, HyTest Ltd., Turku Finland; GTX74203, GTX75071, GeneTex, Inc., San Antonio, TX; 855.020.005, Diaclone, Stamford, CT; XP-5182, ProSci, Inc., Poway, CA; ab10751, Abcam, Inc., Cambridge, UK.; ab16235, Novus Biologicals, Littleton, CO.

[0044] IL-2 can also be defined by its ability to binds an IL-2 receptor as disclosed in U.S. Pat No. 6,955,807. Furthermore, IL-2 can be defined by its biological activity using any suitable assay known in the art. Example of such assays include PHA blast proliferation and NK cell proliferation assays as disclosed in U.S. Pat No 6,955,807.

[0045] IL-2 as used herein is also includes biologically active fragments or variants of IL-2 that show substantial relative activity compared to native IL-2. For example, compounds that show full activity when bound to cells expressing the IL-2 receptor $\alpha\beta\gamma$, but reduced activity on cells bearing IL-2 receptor $\beta\gamma$ (e.g., NK cells) are deemed IL-2 as defined herein. Examples of IL-2 variants that meet this definition of IL-2 are disclosed in U.S. Pat No 6,559,807.

[0046] The term “depression” includes any form of depression as clinically diagnosed by a professional. For instance, this term encompasses major depression, which is characterized by the presence of five or more of the following symptoms for at least 2 weeks: trouble sleeping or excessive sleeping; a dramatic change in appetite, often with weight gain or loss; fatigue and lack of energy; feelings of worthlessness, self-hate, and inappropriate guilt; extreme difficulty concentrating; agitation, restlessness, and irritability; inactivity and withdrawal from usual activities, a loss of interest or pleasure in activities that were once enjoyed (e.g., sexual intercourse); feelings of hopelessness and helplessness; and thoughts of death or suicide.

[0047] The term depression also encompasses dysthymia, a chronic form of depression, characterized by moods that are consistently low, but not as extreme as other types of depression. Patients affected by dysthymia struggle nearly every day with low self-esteem, despair, and hopelessness. The main symptom of dysthymia is low, dark, or sad mood nearly every day for at least 2 years. Other symptoms can include: poor appetite or overeating; insomnia or hypersomnia; low energy or fatigue; low self-esteem; poor concentration; and feelings of hopelessness.

[0048] The term depression also encompasses minor depression, which includes disorders with depressive features that do not meet the criteria for any specific mood disorder or

adjustment disorder with depressed mood. Examples of minor depression may include but are not limited to a recurrent, mild, depressive disturbance that does not meet the criteria for dysthymia; or non-stress-related depressive episodes that do not meet the criteria for a major depressive episode.

5 [0049] The term “cortisol” refers to a family of compositions also referred to as hydrocortisone, and any synthetic or natural analogues thereof. Normal cortisol levels fluctuate throughout the day, typically being less than 25 mg/dl in the morning, and between 5-15mg/dl in the afternoon.

10 [0050] The term “glucocorticoid receptor (GR)” refers to a family of intracellular receptors also referred to as the cortisol receptor, which specifically bind to cortisol and/or cortisol analogs. The term includes isoforms of GR, recombinant GR, and mutated GR.

15 [0051] The term “mifepristone” refers to a family of compositions also referred to as RU486, or RU38.486, or 17-beta-hydroxy-11-beta-(4-dimethyl-aminophenyl)-17-alpha-(1-propynyl)-estra-4,9-dien-3-one), or 11-beta-(4dimethylaminophenyl)-17-beta-hydroxy-17-alpha-(1-propynyl)-estra-4,9-dien-3-one), or analogs thereof, which bind to the GR, typically with high affinity, and inhibit the biological effects initiated/ mediated by the binding of any cortisol or cortisol analogue to a GR receptor. Chemical names for RU-486 vary; for example, RU486 has also been termed: 11β -[p-(Dimethylamino)phenyl]-17 β -hydroxy-17-(1-propynyl)-estra-4,9-dien-3-one; 11β -(4-dimethyl-aminophenyl)-17 β -hydroxy-17 α -(prop-1-ynyl)-estra-4,9-dien-3-one; 17 β -hydroxy-11 β -(4-dimethylaminophenyl-1)-17 α -(propynyl-1)-estra-4,9-diene-3-one; 17 β -hydroxy-11 β -(4-dimethylaminophenyl-1)-17 α -(propynyl-1)-E; (11β ,17 β)-11-[4-dimethylamino)- phenyl]-17-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one; and 11β -[4-(N,N-dimethylamino) phenyl]-17 α -(prop-1-ynyl)-D-4,9-estradiene-17 β -ol-3-one.

25 [0052] The term “specific glucocorticoid receptor antagonist” refers to any composition or compound which partially or completely inhibits (antagonizes) the binding of a glucocorticoid receptor (GR) agonist, such as cortisol, or cortisol analogs, synthetic or natural, to a GR. By “specific,” it is intended that the drug to preferentially bind to the GR rather than the mineralocorticoid receptor (MR) with an affinity at least 100-fold, and
30 frequently 1000-fold.

[0053] A patient "not otherwise in need of treatment with a glucocorticoid receptor antagonist" is a patient who is not suffering from a condition that is known in the art to be effectively treatable with glucocorticoid receptor antagonists. Conditions known in the art to be effectively treatable with glucocorticoid receptor antagonists include Cushing's disease,
5 drug withdrawal, psychosis, dementia, stress disorders, and psychotic major depression.

[0054] In this application, when two therapeutic agents are "administered coextensively," the administration time periods of the agents may completely overlap or at least in part overlap. When the administration of the two agents is not coextensive, the two therapeutic agents are preferably administered in time periods that do not overlap, but still within each
10 other's bioactive period, *i.e.*, the earlier administered agent retains at least a substantial portion of its biological activity in the patient at the time when the latter administered agent is delivered. In other cases where two therapeutic agents are not administered coextensively, however, the two agents may be administered outside of each other's bioactive period.

[0055] Where substituent groups are specified by their conventional chemical formulae,
15 written from left to right, they equally encompass the chemically identical substituents that would result from writing the structure from right to left, *e.g.*, $-\text{CH}_2\text{O}-$ is equivalent to $-\text{OCH}_2-$.

[0056] The term "alkylene" by itself or as part of another substituent means a divalent radical derived from an alkane, as exemplified, but not limited, by $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$, and further includes those groups described below as "heteroalkylene." Typically, an alkyl (or
20 alkylene) group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being preferred in the present invention. A "lower alkyl" or "lower alkylene" is a shorter chain alkyl or alkylene group, generally having eight or fewer carbon atoms.

[0057] The term "alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight (*i.e.*, unbranched) or branched chain, or cyclic hydrocarbon radical, or
25 combination thereof, which may be fully saturated, mono- or polyunsaturated and can include di- and multivalent radicals, having the number of carbon atoms designated (*i.e.*, $\text{C}_1\text{-C}_{10}$ means one to ten carbons). Examples of saturated hydrocarbon radicals include, but are not limited to, groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, cyclohexyl, (cyclohexyl)methyl, cyclopropylmethyl, homologs and isomers of, for
30 example, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. An unsaturated alkyl group is one having one or more double bonds or triple bonds. Examples of unsaturated alkyl groups include, but are not limited to, vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-

pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butyryl, and the higher homologs and isomers. Alkyl groups that are limited to hydrocarbon groups are termed "homoalkyl".

[0058] The term "heteroalkyl," by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or cyclic hydrocarbon radical, or combinations thereof, consisting of the stated number of carbon atoms and at least one heteroatom selected from the group consisting of O, N, P, Si, and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N, P, S, and Si may be placed at any interior position of the heteroalkyl group or at the position at which the alkyl group is attached to the remainder of the molecule. Examples include, but are not limited to, $-\text{CH}_2-\text{CH}_2-\text{O}-\text{CH}_3$, $-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CH}_3$, $-\text{CH}_2-\text{CH}_2-\text{N}(\text{CH}_3)-\text{CH}_3$, $-\text{CH}_2-\text{S}-\text{CH}_2-\text{CH}_3$, $-\text{CH}_2-\text{CH}_2-\text{S}(\text{O})-\text{CH}_3$, $-\text{CH}_2-\text{CH}_2-\text{S}(\text{O})_2-\text{CH}_3$, $-\text{CH}=\text{CH}-\text{O}-\text{CH}_3$, $-\text{Si}(\text{CH}_3)_3$, $-\text{CH}_2-\text{CH}=\text{N}-\text{OCH}_3$, $-\text{CH}=\text{CH}-\text{N}(\text{CH}_3)-\text{CH}_3$, $\text{O}-\text{CH}_3$, $-\text{O}-\text{CH}_2-\text{CH}_3$, and $-\text{CN}$. Up to two heteroatoms may be consecutive, such as, for example, $-\text{CH}_2-\text{NH}-\text{OCH}_3$ and $-\text{CH}_2-\text{O}-\text{Si}(\text{CH}_3)_3$. Similarly, the term "heteroalkylene" by itself or as part of another substituent means a divalent radical derived from heteroalkyl, as exemplified, but not limited by, $-\text{CH}_2-\text{CH}_2-\text{S}-\text{CH}_2-\text{CH}_2-$ and $-\text{CH}_2-\text{S}-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CH}_2-$. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (e.g., alkyleneoxy, alkylenedioxy, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied by the direction in which the formula of the linking group is written. For example, the formula $-\text{C}(\text{O})_2\text{R}'$ represents both $-\text{C}(\text{O})_2\text{R}'$ and $-\text{R}'\text{C}(\text{O})_2$. As described above, heteroalkyl groups, as used herein, include those groups that are attached to the remainder of the molecule through a heteroatom, such as $-\text{C}(\text{O})\text{R}'$, $-\text{C}(\text{O})\text{NR}'$, $-\text{NR}'\text{R}''$, $-\text{OR}'$, $-\text{SR}'$, and/or $-\text{SO}_2\text{R}'$. Where "heteroalkyl" is recited, followed by recitations of specific heteroalkyl groups, such as $-\text{NR}'\text{R}''$ or the like, it will be understood that the terms heteroalkyl and $-\text{NR}'\text{R}''$ are not redundant or mutually exclusive. Rather, the specific heteroalkyl groups are recited to add clarity. Thus, the term "heteroalkyl" should not be interpreted herein as excluding specific heteroalkyl groups, such as $-\text{NR}'\text{R}''$ or the like.

[0059] Unless otherwise explicitly stated, the terms "cycloalkyl" and "heterocycloalkyl," by themselves or in combination with other terms, represent cyclic versions of "alkyl" and "heteroalkyl," respectively. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Examples of

cycloalkyl include, but are not limited to, cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like. Examples of heterocycloalkyl include, but are not limited to, 1-(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, 5 tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, and the like.

[0060] The term "aryl" means, unless otherwise stated, a polyunsaturated, aromatic, hydrocarbon substituent that can be a single ring or multiple rings (preferably from 1 to 3 rings) which are fused together or linked covalently. The term "heteroaryl" refers to aryl groups (or rings) that contain from one to four heteroatoms selected from N, O, and S, 10 wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. A heteroaryl group can be attached to the remainder of the molecule through a carbon or heteroatom. Non-limiting examples of aryl and heteroaryl groups include phenyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5- 15 thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxalyl, 5-quinoxalyl, 3-quinolyl, and 6-quinolyl.

[0061] Each of the above terms (*e.g.*, "alkyl," "heteroalkyl," "aryl," and "heteroaryl") are 20 meant to include both substituted and unsubstituted forms of the indicated radical. Preferred substituents for each type of radical are provided below.

[0062] Substituents for the alkyl and heteroalkyl radicals (including those groups often referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) can be one or more of a variety of 25 groups selected from, but not limited to: -OR', =O, =NR', =N-OR', -NR'R'', -SR', -halogen, -SiR'R''R''', OC(O)R', -C(O)R', -CO₂R', -CONR'R'', -OC(O)NR'R'', -NR''C(O)R', NR' C(O)NR''R''', -NR''C(O)R', -NR-C(NR'R''R''')=NR''', NR C(NR'R'')=NR'', -S(O)R', -S(O)₂R', -S(O)₂NR'R'', NRSO₂R', -CN and -NO₂ in a number ranging from zero to (2m'+1), where m' is the total number of carbon atoms in such radical. R', R'', R''' and R'''' each 30 preferably independently refer to hydrogen, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl (*e.g.*, aryl substituted with 1-3 halogens), substituted or

unsubstituted alkyl, alkoxy or thioalkoxy groups, or arylalkyl groups. When a compound of the invention includes more than one R group, for example, each of the R groups is independently selected as are each R', R'', R''' and R'''' groups when more than one of these groups is present. When R' and R'' are attached to the same nitrogen atom, they can be
 5 combined with the nitrogen atom to form a 4-, 5-, 6-, or 7-membered ring. For example, -NR'R'' is meant to include, but not be limited to, 1-pyrrolidinyl and 4-morpholinyl. From the above discussion of substituents, one of skill in the art will understand that the term "alkyl" is meant to include groups including carbon atoms bound to groups other than hydrogen groups, such as haloalkyl (e.g., -CF₃ and -CH₂CF₃) and acyl (e.g., -C(O)CH₃, -C(O)CF₃, -
 10 C(O)CH₂OCH₃, and the like).

[0063] Similar to the substituents described for the alkyl radical, substituents for the aryl and heteroaryl groups are varied and are selected from, for example: halogen, OR', -NR'R'', -SR', -halogen, -SiR'R''R''', OC(O)R', -C(O)R', CO₂R', -CONR'R'', -OC(O)NR'R'', -NR''C(O)R', NR' C(O)NR''R''', -NR''C(O)₂R', NR-C(NR'R''R''')=NR''', NR
 15 C(NR'R'')=NR''', -S(O)R', -S(O)₂R', -S(O)₂NR'R'', NRSO₂R', -CN and -NO₂, -R', -N₃, -CH(Ph)₂, fluoro(C₁-C₄)alkoxy, and fluoro(C₁-C₄)alkyl, in a number ranging from zero to the total number of open valences on the aromatic ring system; and where R', R'', R''' and R'''' are preferably independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or
 20 unsubstituted heterocycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl. When a compound of the invention includes more than one R group, for example, each of the R groups is independently selected as are each R', R'', R''' and R'''' groups when more than one of these groups is present.

II. DETERMINATION OF DEPRESSIVE SYMPTOMS

25 [0064] Depression diagnosis is primarily based on examination of a patient, by a professional, for symptoms that are indicative of a clinical depression. An objective assessment of depression can be made using rating scales known to persons of skill in the art (e.g., Hamilton Rating Scale for Depression). See, *J. Operational Psychiatry* 10(2):149-165 (1979). The depressive symptoms may represent either major clinical depression, dysthymia,
 30 or minor depressive episodes, each of which is discussed more fully below.

[0065] Major depression can be either a single episode or recurrent, which is the presence of two or more major depressive episodes. The symptoms of major depression cause

clinically significant distress or impairment in social, occupational, or other important areas of functioning. A diagnosis of major depression is characterized by the presence of five (or more) symptoms during the same 2-week period and represents a change from previous functioning, and at least one of the symptoms must be either a depressed mood, or a loss of interest or pleasure. Symptoms characterizing major depression include: (1) depressed mood most of the day, nearly every day, as indicated by either a subjective report (*e.g.*, feeling sad or empty), or observations made by others, *e.g.*, appearing tearful (in children and adolescents, the depressed mood can also be an irritable mood); (2) markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others); (3) significant weight loss when not dieting, or weight gain (*e.g.*, a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day (in children, failure to make expected weight gains should be considered); (4) insomnia or hypersomnia nearly every day; (5) psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down); (6) fatigue or loss of energy nearly every day; (7) feelings of worthlessness or excessive or inappropriate guilt nearly every day (not merely self-reproach or guilt about being sick); (8) diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others); and (9) recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

[0066] A diagnosis of major depression requires that the patient not have previously experienced a manic episode, a mixed episode, or a hypomanic episode. This exclusion, however, does not apply if all of the manic-like, mixed-like, or hypomanic-like episodes were substance or treatment induced, or were due to the direct physiological effects of a general medical condition. Major depression is best characterized as not being better accounted for by schizoaffective disorder and is not superimposed on schizophrenia, schizophreniform disorder, delusional disorder, or a psychotic disorder not otherwise specified.

[0067] The symptoms of dysthymic disorder cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. Dysthymic disorder is best characterized as a depressed mood for most of the day, and for more days than not, as indicated either by a subjective account, or observation by others for at least two years. In children and adolescents, the mood can manifest as irritability and the duration

must be at least one year. In addition to a depressed mood, a diagnosis of dysthymic disorder requires the presence of two (or more) of the following: poor appetite or overeating; insomnia or hypersomnia; low energy or fatigue; low self-esteem; poor concentration or difficulty making decisions; and feelings of hopelessness. During the two-year period of the disturbance for adults (one year for children or adolescents), the person has never been without the symptoms for more than two months at a time. Furthermore, it must be ruled out that the symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).

[0068] For a diagnosis of dysthymic disorder, the patient cannot have experienced a major depressive episode during the first two-years of the dysthymic disturbance (one year for children and adolescents). In other words, the disturbance is not better accounted for by chronic major depressive disorder, or major depressive disorder, in partial remission. There may have been a previous major depressive episode provided there was a full remission (no significant signs or symptoms for 2 months) before development of the dysthymic disorder.

In addition, after the initial 2 years (1 year in children or adolescents) of dysthymic disorder, there may be superimposed episodes of major depressive disorder, in which case both diagnoses may be given when the criteria are met for a major depressive episode.

[0069] A diagnosis of dysthymic disorder requires that the patient not have previously experienced a manic episode, a mixed episode, or a hypomanic episode, and criteria for cyclothymic disorder have not been met. Nor, does the disturbance occur exclusively during the course of a chronic psychotic disorder, such as schizophrenia or delusional disorder.

[0070] Minor depression includes mood disorders with depressive features that do not meet the criteria for any specific mood disorder or adjustment disorder with depressed mood.

Examples of minor depression may include but are not limited to a recurrent, mild, depressive episode that does not meet the criteria for dysthymia, or a non-stress-related depressive episode that does not meet the criteria for a major depressive episode.

III. GENERAL LABORATORY PROCEDURES

[0071] When practicing the methods of the invention, a number of general laboratory tests can be used to assist in the progress of the patient undergoing IL-2 therapy, including monitoring of parameters such as blood cortisol, drug metabolism, *etc.* These procedures can be helpful because all patients metabolize and react to drugs uniquely. In addition, such

monitoring may be important because each GR antagonist has different pharmacokinetics. Patients with different medical conditions may require different dosage regimens and formulations. Such procedures and means for determining dosage regimens and formulations are well described in the scientific and patent literature.

5 **A. Determining Blood Cortisol Levels**

[0072] Varying levels of blood cortisol have been associated with IL-2-induced depression, however, the invention may also be practiced upon patients with apparently normal levels of blood cortisol. Thus, monitoring blood cortisol and determining baseline cortisol levels are useful laboratory tests to assist in monitoring the progress of patients undergoing IL-2
10 therapy. A wide variety of laboratory tests exist that can be used to determine whether an individual is normal, hypo- or hypercortisolemic. Patients who are to receive or have been receiving long term IL-2 treatment typically have normal levels of cortisol that are often less than 25 µg/dl in the morning, and frequently about 15 µg/dl or less in the afternoon, which is considered to be at the high end of the normal range of 5-15 µg/dl in the afternoon.

15 [0073] Immunoassays such as radioimmunoassays are commonly used because they are accurate, easy to do and relatively cheap. Because levels of circulating cortisol are an indicator of adrenocortical function, a variety of stimulation and suppression tests, such as ACTH Stimulation, ACTH Reserve, or dexamethasone suppression (see, *e.g.*, Greenwald, *Am. J. Psychiatry* 143:442-446, 1986), can also provide diagnostic, prognostic or other
20 information to be used adjunctively in the methods of the invention.

[0074] One such assay available in kit form is the radioimmunoassay available as “Double Antibody Cortisol Kit” (Diagnostic Products Corporation, Los Angeles, CA), (*Acta Psychiatr. Scand.* 70:239-247, 1984). This test is a competitive radioimmunoassay in which ¹²⁵I-labeled cortisol competes with cortisol from a clinical sample for antibody sites. In this
25 test, due to the specificity of the antibody and lack of any significant protein effect, serum and plasma samples require neither pre-extraction nor pre-dilution.

B. Determination of Blood/Urine Mifepristone Levels

[0075] Because a patient’s metabolism, clearance rate, toxicity levels, etc. differs with variations in underlying primary or secondary disease conditions, drug history, age, general
30 medical condition and the like, it may be necessary to measure blood and urine levels of GR antagonist. Means for such monitoring are well described in the scientific and patent

literature. As in one embodiment of the invention, mifepristone is administered to ameliorate the symptoms of depression in a patient undergoing IL-2 therapy, an illustrative example of determining blood and urine mifepristone levels is set forth in the Example below.

C. Other Laboratory Procedures

5 [0076] Because the mechanism of depression associated with IL-2 therapy is complex and the symptoms may vary, a number of additional laboratory tests can be used adjunctively in the methods of the invention to assist in diagnosis, treatment planning, prognosis, toxicity, and the like. For example, diagnosis and treatment assessment can be augmented by monitoring and measuring glucocorticoid-sensitive variables, including but not limited to
10 fasting blood sugar, blood sugar after oral glucose administration, plasma concentrations thyroid stimulating hormone (TSH), corticosteroid-binding globulin, luteinizing hormone (LH), testosterone-estradiol-binding globulin, leptin, insulin, and/or total and free testosterone.

[0077] Laboratory tests monitoring and measuring GR antagonist metabolite generation,
15 plasma concentrations and clearance rates, including urine concentration of antagonist and metabolites, may also be useful in practicing the methods of the invention. For example, mifepristone has two hydrophilic, N-monomethylated and N-dimethylated, metabolites. Plasma and urine concentrations of these metabolites (in addition to RU486) can be determined using, for example, thin layer chromatography, as described in Kawai,
20 *Pharmacol. and Experimental Therapeutics* 241:401-406, 1987.

IV. GLUCOCORTICOID RECEPTOR ANTAGONISTS TO AMELIORATE SYMPTOMS OF DEPRESSION IN PATIENTS UNDERGOING IL-2 THERAPY

[0078] The invention provides for methods of inhibiting or reversing the symptoms of
25 depression induced by IL-2 therapy utilizing any composition or compound that can block or interfere with the binding of cortisol or a cortisol analogue to a GR. Antagonists of GR activity utilized in the methods of the invention are well described in the scientific and patent literature. A few illustrative examples are set forth below.

A. Steroidal Anti-Glucocorticoids as GR Antagonists

[0079] Steroidal glucocorticoid antagonists are administered to inhibit or reverse IL-2-induced depression in various embodiments of the invention. Steroidal antiglucocorticoids can be obtained by modification of the basic structure of glucocorticoid agonists, *i.e.*, varied forms of the steroid backbone. The structure of cortisol can be modified in a variety of ways. The two most commonly known classes of structural modifications of the cortisol steroid backbone to create glucocorticoid antagonists include modifications of the 11-beta hydroxy group and modification of the 17-beta side chain (see, *e.g.*, Lefebvre, *J. Steroid Biochem.* 33:557-563, 1989).

[0080] Examples of steroidal GR antagonists include androgen-type steroid compounds as described in US Patent No. 5,929,058, and the compounds disclosed in US Patent Nos. 4,296,206; 4,386,085; 4,447,424; 4,477,445; 4,519,946; 4,540,686; 4,547,493; 4,634,695; 4,634,696; 4,753,932; 4,774,236; 4,808,710; 4,814,327; 4,829,060; 4,861,763; 4,912,097; 4,921,638; 4,943,566; 4,954,490; 4,978,657; 5,006,518; 5,043,332; 5,064,822; 5,073,548; 5,089,488; 5,089,635; 5,093,507; 5,095,010; 5,095,129; 5,132,299; 5,166,146; 5,166,199; 5,173,405; 5,276,023; 5,380,839; 5,348,729; 5,426,102; 5,439,913; 5,616,458, and 5,696,127. Such steroidal GR antagonists include cortexolone, dexamethasone-oxetanone, 19-nordeoxycorticosterone, 19-norprogesterone, cortisol-21-mesylate; dexamethasone-21-mesylate, 11 β -(4-dimethylaminoethoxyphenyl)-17 α -propynyl-17 β -hydroxy-4,9 estradien-3-one (RU009), and 17 β -hydroxy-17 α -19-(4-methylphenyl)androsta-4,9(11)-dien-3-one (RU044).

1. Removal or Substitution of the 11-beta Hydroxy Group

[0081] Glucocorticoid agonists with modified steroidal backbones comprising removal or substitution of the 11-beta hydroxy group are administered in one embodiment of the invention. This class includes natural antiglucocorticoids, including cortexolone, progesterone and testosterone derivatives, and synthetic compositions, such as mifepristone (Lefebvre *et al.*, *supra*). Preferred embodiments of the invention include all 11-beta-aryl steroid backbone derivatives because these compounds are devoid of progesterone receptor (PR) binding activity (Agarwal, *FEBS* 217:221-226, 1987). Another preferred embodiment comprises an 11-beta phenyl-aminodimethyl steroid backbone derivative, *i.e.*, mifepristone, which is both an effective anti-glucocorticoid and anti-progesterone agent. These

compositions act as reversibly-binding steroid receptor antagonists. For example, when bound to a 11-beta phenyl-aminodimethyl steroid, the steroid receptor is maintained in a conformation that cannot bind its natural ligand, such as cortisol in the case of GR (Cadepond, 1997, *supra*).

- 5 [0082] Synthetic 11-beta phenyl-aminodimethyl steroids include mifepristone, also known as RU486, or 17-beta-hydrox-11-beta-(4-dimethyl-aminophenyl)17-alpha-(1-propynyl)estra-4,9-dien-3-one). Mifepristone has been shown to be a powerful antagonist of both the progesterone and glucocorticoid (GR) receptors. Another 11-beta phenyl-aminodimethyl steroids shown to have GR antagonist effects includes RU009 (RU39.009), 11-beta-(4-
- 10 dimethyl-aminoethoxyphenyl)-17-alpha-(propynyl-17 beta-hydroxy-4,9-estradien-3-one) (see Bocquel, *J. Steroid Biochem. Molec. Biol.* **45**:205-215, 1993). Another GR antagonist related to RU486 is RU044 (RU43.044) 17-beta-hydrox-17-alpha-19-(4-methyl-phenyl)-androsta-4,9 (11)-dien-3-one) (Bocquel, 1993, *supra*). See also Teutsch, *Steroids* 38:651-665, 1981; U.S. Patent Nos. 4,386,085 and 4,912,097.
- 15 [0083] One embodiment includes compositions containing the basic glucocorticoid steroid structure which are irreversible anti-glucocorticoids. Such compounds include alpha-keto-methanesulfonate derivatives of cortisol, including cortisol-21-mesylate (4-pregnene-11-beta, 17- alpha, 21-triol-3, 20-dione-21-methane-sulfonate and dexamethasone-21-mesylate (16-methyl-9 alpha-fluoro-1,4-pregnadiene-11 beta, 17- alpha, 21-triol-3, 20-dione-21-methane-
- 20 sulfonate). See Simons, *J. Steroid Biochem.* 24:25-32, 1986; Mercier, *J. Steroid Biochem.* 25:11-20, 1986; U.S. Patent No. 4,296,206.

2. Modification of the 17-beta Side Chain Group

- [0084] Steroidal antiglucocorticoids which can be obtained by various structural modifications of the 17-beta side chain are also used in the methods of the invention. This
- 25 class includes synthetic antiglucocorticoids such as dexamethasone-oxetanone, various 17, 21-acetonide derivatives and 17-beta-carboxamide derivatives of dexamethasone (Lefebvre, 1989, *supra*; Rousseau, *Nature* 279:158-160, 1979).

3. Other Steroid Backbone Modifications

- [0085] GR antagonists used in the various embodiments of the invention include any
- 30 steroid backbone modification which effects a biological response resulting from a GR-agonist interaction. Steroid backbone antagonists can be any natural or synthetic variation of

cortisol, such as adrenal steroids missing the C-19 methyl group, such as 19-nordeoxycorticosterone and 19-norprogesterone (Wynne, *Endocrinology* 107:1278-1280, 1980).

[0086] In general, the 11-beta side chain substituent, and particularly the size of that substituent, can play a key role in determining the extent of a steroid's antiglucocorticoid activity. Substitutions in the A ring of the steroid backbone can also be important. 17-hydroxypropenyl side chains generally decrease antiglucocorticoid activity in comparison to 17-propinyl side chain containing compounds.

[0087] Additional glucocorticoid receptor antagonists known in the art and suitable for practice of the invention include 21-hydroxy-6,19-oxidoprogesterone (see Vicent, *Mol. Pharm.* 52:749-753, 1997); ORG 31710, (6 β ,11 β ,17 β)-11-(4-(dimethyl-amino)phenyl)-6-methyl-4',5'-dihydro[estra-4,9-diene-17,2'(3H')-furan]-3-one, (see Mizutani, *J Steroid Biochem Mol Biol* 42(7):695-704, 1992); ORG 34517, (11 β ,17 β)-11-(1,3-benzodioxol-5-yl)-17-hydroxy-17-(1-propynyl)-estra-4,9-dien-3-one, as disclosed in Hoyberg et al., *Int'l J. of Neuro-psychopharmacology*, 5:Supp. 1, S148 (2002); ORG 33628, [(11 β ,17 α)-11-(4-acetylphenyl)-17,23-epoxy-19,24-dinorchola-4,-9,20-trien-3-one]; ORG 31806, [(7 β ,11 β ,17 β)-11-(4-(dimethylamino)phenyl)-7-Me-4',5'-dihydrospiro(oestra-4,9-diene-17,2'(3H)-furan)-3-one]-; ORG 34116, (11 β , 17 α)-11,21-Bis[4-(dimethylamino)phenyl]-17-hydroxy-19-norpregna-4,9,dien-20-yn-3-one; ORG 34850, (11b,17a)-11-[4-(dimethylamino)phenyl]-17-hydroxy-21-[4-(methylsulfonyl)phenyl]-19-norpregna-4,9-dien-20-yn-3-one, and related compounds disclosed in U.S. Pat. 5,741,787; RU43044, (17 β -hydroxy-11 β -4-[methyl]-[1-methylehtyl]aminophenyl/-17 α -[prop-1-ynyl]estra-4-9-diene-3-one ("RU40555", see Kim, *J Steroid Biochem Mol Biol.* 67(3):213-22, 1998), RU28362, and ZK98299.

B. Non-Steroidal Anti-Glucocorticoids as Antagonists

[0088] Non-steroidal glucocorticoid antagonists are also used in the methods of the invention to inhibit or reverse IL-2-induced depression. These include synthetic mimetics and analogs of proteins, including partially peptidic, pseudopeptidic and non-peptidic molecular entities. For example, oligomeric peptidomimetics useful in the invention include (alpha-beta-unsaturated) peptidosulfonamides, N-substituted glycine derivatives, oligo carbamates, oligo urea peptidomimetics, hydrazinopeptides, oligosulfones and the like (see,

- e.g.*, Amour, *Int. J. Pept. Protein Res.* 43:297-304, 1994; de Bont, *Bioorganic & Medicinal Chem.* 4:667-672, 1996). The creation and simultaneous screening of large libraries of synthetic molecules can be carried out using well-known techniques in combinatorial chemistry, for example, see van Breemen, *Anal Chem* 69:2159-2164, 1997; and Lam,
- 5 *Anticancer Drug Des* 12:145-167, 1997. Design of peptidomimetics specific for GR can be designed using computer programs in conjunction with combinatorial chemistry (combinatorial library) screening approaches (Murray, *J. of Computer-Aided Molec. Design* 9:381-395, 1995; Bohm, *J. of Computer-Aided Molec. Design* 10:265-272, 1996). Such “rational drug design” can help develop peptide isomers and conformers including
- 10 cycloisomers, retro-inverso isomers, retro isomers and the like (as discussed in Chorev, *TibTech* 13:438-445, 1995).
- [0089]** Examples of non-steroidal GR antagonists include ketoconazole, clotrimazole; N (triphenylmethyl)imidazole; N-([2-fluoro-9-phenyl]fluorenyl)imidazole; N-([2-pyridyl]diphenylmethyl)imidazole; N (2 [4,4',4"-trichlorotrityl]oxyethyl)morpholine; 1-
- 15 (2[4,4',4"-trichlorotrityl]oxyethyl)-4 (2 hydroxyethyl)piperazine dimaleate; N-([4,4',4"-trichlorotrityl)imidazole; 9-(3-mercapto-1,2,4 triazolyl)-9-phenyl-2,7-difluorofluorenone; 1-(2-chlorotrityl)-3,5-dimethylpyrazole; 4 (morpholinomethyl)-A-(2-pyridyl)benzhydrol; 5-(5-methoxy-2-(N-methylcarbamoyl)-phenyl)dibenzosuberol; N-(2-chlorotrityl)-L-prolinol acetate; 1-(2-chlorotrityl)-2-methylimidazole; 1 (2 chlorotrityl)-1,2,4-triazole; 1,S-bis(4,4',4"-
- 20 trichlorotrityl)-1,2,4-triazole-3-thiol; and N ((2,6 dichloro-3-methylphenyl)diphenyl)methylimidazole (see US Patent No. 6,051,573); the GR antagonist compounds disclosed in US Patent No. 5,696,127; the glucocorticoid receptor antagonists disclosed in Bradley et al., *J. Med. Chem.* 45, 2417-2424 (2002), *e.g.*, 4a(S)-Benzyl-2(R)-chloroethynyl-1,2,3,4,4a,9,10,10a(R)-octahydro-phenanthrene-2,7-diol (CP 394531) and
- 25 4a(S)-Benzyl-2(R)-prop-1-ynyl-1,2,3,4,4a,9,10,10a(R)-octahydro-phenanthrene-2,7-diol (CP 409069); the compounds disclosed in PCT International Application No. WO 96/19458, which describes non-steroidal compounds which are high-affinity, highly selective antagonists for steroid receptors, such as 6-substituted-1,2-dihydro-N protected-quinolines; and some κ opioid ligands, such as the κ opioid compounds dynorphin-1,13 diamide,
- 30 U50,488 (trans-(1R,2R)-3,4-dichloro-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzeneacetamide), bremazocine and ethylketocyclazocine; 4b(S)-benzyl-7(S)-hydroxy-7-(1-propynyl)-4b,5,6,7,8,8a(R),9,10-octahydrophenanthrene-2-carboxylic acid (pyridine-4-ylmethyl)amide CP-472555), 4b(S)-benzyl-7(S)-hydroxy-7-

(3,3,3-trifluoropropyl)-4b,5,6,7,8,8a(R),9,10-octahydrophenanthrene-2-carboxylic acid (2-methylpyridin-3-ylmethyl)amide and related compounds disclosed in WO 0066522 and in U.S. Pat App. 20040176595; octahydrophenanthrenyl carbamates disclosed in EP 1201649; oxadiazolylalkoxyoctahydrophenanthrenes disclosed in EP 1201660; octahydrophenanthrene
 5 hydrazines as disclosed in WO 2005/047254; modulators of the glucocorticoid receptor as disclosed in WO 2004/005299; tricyclic compounds disclosed in WO 2005/011336 and WO 2005/011337; Wieland-Miescher ketone derivatives disclosed in WO 2003/011755; cyclopent[f]indazole and benz[f]indazole derivatives disclosed WO 2004/075840; spirocyclic compounds disclosed in WO 2004/093805; octahydro-2-H-naphtho[1,2,-f]indole-4-
 10 carboxamide derivatives disclosed in WO 2004/026248; cholic acid derivatives disclosed in WO 2004/000869; dibenzopyran derivatives disclosed in WO 2001/16128; 6H-dibenzo[b,d]pyran derivatives disclosed in U.S. Pat App. 20020049322 and U.S. Pat App. 20030220332, substituted aminobenzene derivatives disclosed in WO 2002/064550; triphenylmethane derivatives disclosed in U.S. Pat No 6,166,013; diphenyl ether derivatives
 15 disclosed in WO 2001/047859 and WO 1999/63976; azadecalin derivatives disclosed in WO 2005/070893; fused ring azadecalins disclosed in WO 2005/087769; the modified pyrimidine compounds disclosed in PCT/US05/23675, and the non-specific opioid receptor ligand, naloxone, as disclosed in Evans *et al.*, *Endocrin.*, 141:2294-2300 (2000).

C. Identifying Specific Glucocorticoid Receptor Antagonists

20 [0090] Because any specific GR antagonist can be used to inhibit or reverse IL-2-induced depression in the methods of the invention, in addition to the compounds and compositions described above, additional useful GR antagonists can be determined by the skilled artisan. A variety of such routine, well-known methods can be used and are described in the scientific and patent literature. They include *in vitro* and *in vivo* assays for the identification of
 25 additional GR antagonists. A few illustrative examples are described below.

[0091] One assay that can be used to identify a GR antagonist of the invention measures the effect of a putative GR antagonist on tyrosine amino-transferase activity in accordance with the method of Granner, *Meth. Enzymol.* 15:633, 1970. This analysis is based on measurement of the activity of the liver enzyme tyrosine amino-transferase (TAT) in cultures
 30 of rat hepatoma cells (RHC). TAT catalyzes the first step in the metabolism of tyrosine and is induced by glucocorticoids (cortisol) both in liver and hepatoma cells. This activity is easily measured in cell extracts. TAT converts the amino group of tyrosine to 2-oxoglutaric

acid. P-hydroxyphenylpyruvate is also formed. It can be converted to the more stable p-hydroxybenzaldehyde in an alkaline solution and quantitated by absorbance at 331 nm. The putative GR antagonist is co-administered with cortisol to whole liver, *in vivo* or *ex vivo*, or hepatoma cells or cell extracts. A compound is identified as a GR antagonist when its administration decreases the amount of induced TAT activity, as compared to control (*i.e.*, only cortisol or GR agonist added) (see also Shirwany, *Biochem. Biophys. Acta* 886:162-168, 1986).

[0092] Further illustrative of the many assays which can be used to identify compositions utilized in the methods of the invention, in addition to the TAT assay, are assays based on glucocorticoid activities *in vivo*. For example, assays that assess the ability of a putative GR antagonist to inhibit uptake of ^3H -thymidine into DNA in cells which are stimulated by glucocorticoids can be used. Alternatively, the putative GR antagonist can compete with ^3H -dexamethasone for binding to a hepatoma tissue culture GR (*see, e.g.*, Choi, *et al.*, *Steroids* 57:313-318, 1992). As another example, the ability of a putative GR antagonist to block nuclear binding of ^3H -dexamethasone-GR complex can be used (Alexandrova *et al.*, *J. Steroid Biochem. Mol. Biol.* 41:723-725, 1992). To further identify putative GR antagonists, kinetic assays able to discriminate between glucocorticoid agonists and antagonists by means of receptor-binding kinetics can also be used (as described in Jones, *Biochem J.* 204:721-729, 1982).

[0093] In another illustrative example, the assay described by Daune, *Molec. Pharm.* 13:948-955, 1977; and in U.S. Patent No. 4,386,085, can be used to identify anti-glucocorticoid activity. Briefly, the thymocytes of adrenalectomized rats are incubated in nutritive medium containing dexamethasone with the test compound (the putative GR antagonist) at varying concentrations. ^3H -uridine is added to the cell culture, which is further incubated, and the extent of incorporation of radiolabel into polynucleotide is measured. Glucocorticoid agonists decrease the amount of ^3H -uridine incorporated. Thus, a GR antagonist will oppose this effect.

[0094] For additional compounds that can be utilized in the methods of the invention and methods of identifying and making such compounds, see U.S. Patent Nos.: 4,296,206 (see above); 4,386,085 (see above); 4,447,424; 4,477,445; 4,519,946; 4,540,686; 4,547,493; 4,634,695; 4,634,696; 4,753,932; 4,774,236; 4,808,710; 4,814,327; 4,829,060; 4,861,763; 4,912,097; 4,921,638; 4,943,566; 4,954,490; 4,978,657; 5,006,518; 5,043,332; 5,064,822;

5,073,548; 5,089,488; 5,089,635; 5,093,507; 5,095,010; 5,095,129; 5,132,299; 5,166,146; 5,166,199; 5,173,405; 5,276,023; 5,380,839; 5,348,729; 5,426,102; 5,439,913; and 5,616,458; U.S. Pat. App. 20040176595, and WO 96/19458, which describes non-steroidal compounds which are high-affinity, highly selective modulators (antagonists) for steroid
5 receptors, such as 6-substituted-1,2-dihydro N-1 protected quinolines.

[0095] The specificity of the antagonist for the GR relative to the MR can be measured using a variety of assays known to those of skill in the art. For example, specific antagonists can be identified by measuring the ability of the antagonist to bind to the GR compared to the MR (see, *e.g.*, U.S. Patent Nos. 5,606,021; 5,696,127; 5,215,916; 5,071,773). Such an
10 analysis can be performed using either direct binding assay or by assessing competitive binding to the purified GR or MR in the presence of a known antagonist. In an exemplary assay, cells that are stably expressing the glucocorticoid receptor or mineralocorticoid receptor (*see, e.g.*, US Patent 5,606,021) at high levels are used as a source of purified receptor. The affinity of the antagonist for the receptor is then directly measured. Those
15 antagonists that exhibit at least a 100-fold higher affinity, often 1000-fold, for the GR relative to the MR are then selected for use in the methods of the invention.

[0096] A GR-specific antagonist may also be defined as a compound that has the ability to inhibit GR-mediated activities, but not MR-mediated activities. One method of identifying such a GR-specific antagonist is to assess the ability of an antagonist to prevent activation of
20 reporter constructs using transfection assays (*see, e.g.*, Bocquel *et al.*, *J. Steroid Biochem Molec. Biol.* 45:205-215, 1993; U.S. Patent Nos. 5,606,021, 5,929,058). In an exemplary transfection assay, an expression plasmid encoding the receptor and a reporter plasmid containing a reporter gene linked to receptor-specific regulatory elements are cotransfected into suitable receptor-negative host cells. The transfected host cells are then cultured in the
25 presence and absence of a hormone, such as cortisol or an analog thereof, able to activate the hormone responsive promoter/enhancer element of the reporter plasmid. Next the transfected and cultured host cells are monitored for induction (*i.e.*, the presence) of the product of the reporter gene sequence. Finally, the expression and/or steroid binding-capacity of the hormone receptor protein (coded for by the receptor DNA sequence on the expression
30 plasmid and produced in the transfected and cultured host cells), is measured by determining the activity of the reporter gene in the presence and absence of an antagonist. The antagonist activity of a compound may be determined in comparison to known antagonists of the GR and MR receptors (*see, e.g.*, U.S. Patent 5,696,127). Efficacy is then reported as the percent

maximal response observed for each compound relative to a reference antagonist compound. A GR-specific antagonist is considered to exhibit at least a 100-fold, often 1000-fold or greater, activity towards the GR relative to the MR.

V. AMELIORATING SYMPTOMS OF DEPRESSION ASSOCIATED WITH IL-2 THERAPY USING GLUCOCORTICOID RECEPTOR ANTAGONISTS

[0097] Antiglucocorticoids, such as mifepristone, are formulated as pharmaceuticals to be used in the methods of the invention to inhibit or reverse IL-2-induced depression. Any composition or compound that can block or interfere with the binding of cortisol or a cortisol analogue to a GR can be used as a pharmaceutical in the invention. Routine means to determine GR antagonist drug regimens and formulations to practice the methods of the invention are well described in the patent and scientific literature, and some illustrative examples are set forth below.

A. Glucocorticoid Receptor Antagonists as Pharmaceutical Compositions

[0098] The GR antagonists used in the methods of the invention can be administered by any means known in the art, *e.g.*, parenterally, topically, orally, or by local administration, such as by aerosol or transdermally. The methods of the invention provide for prophylactic and/or therapeutic treatments. The GR antagonists as pharmaceutical formulations can be administered in a variety of unit dosage forms depending upon the condition or disease and the degree of severity, the general medical condition of each patient, the resulting preferred method of administration and the like. Details on techniques for formulation and administration are well described in the scientific and patent literature, see, *e.g.*, the latest edition of *Remington's Pharmaceutical Sciences*, Mack Publishing Co, Easton PA. Therapeutically effective amounts of glucocorticoid blockers suitable for practice of the method of the invention may range from about 0.5 to about 25 milligrams per kilogram (mg/kg). A person of ordinary skill in the art will be able without undue experimentation, having regard to that skill and this disclosure, to determine a therapeutically effective amount of a particular glucocorticoid blocker compound for practice of this invention.

[0099] In general, glucocorticoid blocker compounds may be administered as pharmaceutical compositions by any method known in the art for administering therapeutic drugs. Compositions may take the form of tablets, pills, capsules, semisolids, powders, sustained release formulations, solutions, suspensions, elixirs, aerosols, or any other

appropriate compositions; and comprise at least one compound of this invention in combination with at least one pharmaceutically acceptable excipient. Suitable excipients are well known to persons of ordinary skill in the art, and they, and the methods of formulating the compositions, may be found in such standard references as *Remington's Pharmaceutical Sciences*. Suitable liquid carriers, especially for injectable solutions, include water, aqueous saline solution, aqueous dextrose solution, and glycols.

[0100] Aqueous suspensions of the invention contain a GR antagonist in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients include a suspending agent, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, and dispersing or wetting agents such as a naturally occurring phosphatide (e.g., lecithin), a condensation product of an alkylene oxide with a fatty acid (e.g., polyoxyethylene stearate), a condensation product of ethylene oxide with a long chain aliphatic alcohol (e.g., heptadecaethylene oxycetanol), a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol (e.g., polyoxyethylene sorbitol mono-oleate), or a condensation product of ethylene oxide with a partial ester derived from fatty acid and a hexitol anhydride (e.g., polyoxyethylene sorbitan mono-oleate). The aqueous suspension can also contain one or more preservatives such as ethyl or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose, aspartame or saccharin. Formulations can be adjusted for osmolality.

[0101] Oil suspensions can be formulated by suspending a GR antagonist in a vegetable oil, such as arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin; or a mixture of these. The oil suspensions can contain a thickening agent, such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents can be added to provide a palatable oral preparation, such as glycerol, sorbitol or sucrose. These formulations can be preserved by the addition of an antioxidant such as ascorbic acid. As an example of an injectable oil vehicle, see Minto, *J. Pharmacol. Exp. Ther.* 281:93-102, 1997. The pharmaceutical formulations of the invention can also be in the form of oil-in-water emulsions. The oily phase can be a vegetable oil or a mineral oil, described above, or a mixture of these. Suitable emulsifying agents include naturally-occurring gums, such as gum acacia and gum tragacanth, naturally occurring phosphatides, such as soybean lecithin, esters or partial esters derived from fatty acids and hexitol anhydrides, such as sorbitan mono-oleate, and condensation products of these partial esters with ethylene oxide, such as

polyoxyethylene sorbitan mono-oleate. The emulsion can also contain sweetening agents and flavoring agents, as in the formulation of syrups and elixirs. Such formulations can also contain a demulcent, a preservative, or a coloring agent.

[0102] Glucocorticoid blocker pharmaceutical formulations can be prepared according to any method known to the art for the manufacture of pharmaceuticals. Such drugs can contain sweetening agents, flavoring agents, coloring agents and preserving agents. Any glucocorticoid blocker formulation can be admixed with nontoxic pharmaceutically acceptable excipients which are suitable for manufacture.

[0103] Typically, glucocorticoid blocker compounds suitable for use in the practice of this invention will be administered orally. The amount of a compound of this invention in the composition may vary widely depending on the type of composition, size of a unit dosage, kind of excipients, and other factors well known to those of ordinary skill in the art. In general, the final composition may comprise from 0.000001 percent by weight (%w) to 10 %w of the glucocorticoid blocker compounds, preferably 0.00001 %w to 1 %w, with the remainder being the excipient or excipients. For example, the GR antagonist mifepristone is given orally in tablet form, with dosages in the range of between about 0.5 and 25 mg/kg, more preferably between about 0.75 mg/kg and 15 mg/kg, most preferably about 10 mg/kg.

[0104] Pharmaceutical formulations for oral administration can be formulated using pharmaceutically acceptable carriers well known in the art in dosages suitable for oral administration. Such carriers enable the pharmaceutical formulations to be formulated in unit dosage forms as tablets, pills, powder, dragees, capsules, liquids, lozenges, gels, syrups, slurries, suspensions, *etc.*, suitable for ingestion by the patient. Pharmaceutical preparations for oral use can be obtained through combination of glucocorticoid blocker compounds with a solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable additional compounds, if desired, to obtain tablets or dragee cores. Suitable solid excipients are carbohydrate or protein fillers and include, but are not limited to sugars, including lactose, sucrose, mannitol, or sorbitol; starch from corn, wheat, rice, potato, or other plants; cellulose such as methyl cellulose, hydroxypropylmethyl-cellulose or sodium carboxymethylcellulose; and gums including arabic and tragacanth; as well as proteins such as gelatin and collagen. If desired, disintegrating or solubilizing agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, alginic acid, or a salt thereof, such as sodium alginate.

[0105] The GR antagonists of this invention can also be administered in the form of suppositories for rectal administration of the drug. These formulations can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperatures and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

[0106] The GR antagonists of this invention can also be administered by in intranasal, intraocular, intravaginal, and intrarectal routes including suppositories, insufflation, powders and aerosol formulations (for examples of steroid inhalants, see Rohatagi, *J. Clin. Pharmacol.* 35:1187-1193, 1995; Tjwa, *Ann. Allergy Asthma Immunol.* 75:107-111, 1995).

[0107] The GR antagonists of the invention can be delivered transdermally, by a topical route, formulated as applicator sticks, solutions, suspensions, emulsions, gels, creams, ointments, pastes, jellies, paints, powders, and aerosols.

[0108] The GR antagonists of the invention can also be delivered as microspheres for slow release in the body. For example, microspheres can be administered via intradermal injection of drug (*e.g.*, mifepristone)-containing microspheres, which slowly release subcutaneously (see Rao, *J. Biomater Sci. Polym.* 7:623-645, 1995; as biodegradable and injectable gel formulations (see, *e.g.*, Gao *Pharm. Res.* 12:857-863, 1995); or, as microspheres for oral administration (see, *e.g.*, Eyles, *J. Pharm. Pharmacol.* 49:669-674, 1997). Both transdermal and intradermal routes afford constant delivery for weeks or months.

[0109] The GR antagonist pharmaceutical formulations of the invention can be provided as a salt and can be formed with many acids, including but not limited to hydrochloric, sulfuric, acetic, lactic, tartaric, malic, succinic, *etc.* Salts tend to be more soluble in aqueous or other protonic solvents that are the corresponding free base forms. In other cases, the preferred preparation may be a lyophilized powder in 1 mM-50 mM histidine, 0.1%-2% sucrose, 2%-7% mannitol at a pH range of 4.5 to 5.5, that is combined with buffer prior to use

[0110] In another embodiment, the GR antagonist formulations of the invention are useful for parenteral administration, such as intravenous (IV) administration. The formulations for administration will commonly comprise a solution of the GR antagonist (*e.g.*, mifepristone) dissolved in a pharmaceutically acceptable carrier. Among the acceptable vehicles and solvents that can be employed are water and Ringer's solution, an isotonic sodium chloride. In addition, sterile fixed oils can conventionally be employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or

diglycerides. In addition, fatty acids such as oleic acid can likewise be used in the preparation of injectables. These solutions are sterile and generally free of undesirable matter. These formulations may be sterilized by conventional, well known sterilization techniques. The formulations may contain pharmaceutically acceptable auxiliary substances
5 as required to approximate physiological conditions such as pH adjusting and buffering agents, toxicity adjusting agents, *e.g.*, sodium acetate, sodium chloride, potassium chloride, calcium chloride, sodium lactate and the like. The concentration of GR antagonist in these formulations can vary widely, and will be selected primarily based on fluid volumes, viscosities, body weight, and the like, in accordance with the particular mode of
10 administration selected and the patient's needs. For IV administration, the formulation can be a sterile injectable preparation, such as a sterile injectable aqueous or oleaginous suspension. This suspension can be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation can also be a sterile injectable solution or suspension in a nontoxic parenterally-acceptable diluent or
15 solvent, such as a solution of 1,3-butanediol.

[0111] In another embodiment, the GR antagonist formulations of the invention can be delivered by the use of liposomes which fuse with the cellular membrane or are endocytosed, *i.e.*, by employing ligands attached to the liposome, or attached directly to the oligonucleotide, that bind to surface membrane protein receptors of the cell resulting in
20 endocytosis. By using liposomes, particularly where the liposome surface carries ligands specific for target cells, or are otherwise preferentially directed to a specific organ, one can focus the delivery of the GR antagonist into the target cells *in vivo*. (See, *e.g.*, Al-Muhammed, *J. Microencapsul.* 13:293-306, 1996; Chonn, *Curr. Opin. Biotechnol.* 6:698-708, 1995; Ostro, *Am. J. Hosp. Pharm.* 46:1576-1587, 1989).

25 **B. Determining Dosing Regimens for Glucocorticoid Receptor Antagonists**

[0112] The methods of this invention inhibit or reverse IL-2-induced depression. The amount of GR antagonist adequate to accomplish this is defined as a "therapeutically effective dose". The dosage schedule and amounts effective for this use, *i.e.*, the "dosing regimen," will depend upon a variety of factors, including the type of the IL-2 medication the
30 patient is using, the severity of IL-2-induced depression that has already occurred, the patient's physical status, age and the like. In calculating the dosage regimen for a patient, the mode of administration also is taken into consideration.

[0113] The dosage regimen also takes into consideration pharmacokinetics parameters well known in the art, *i.e.*, the GR antagonists' rate of absorption, bioavailability, metabolism, clearance, and the like (see, *e.g.*, Hidalgo-Aragones, *J. Steroid Biochem. Mol. Biol.* 58:611-617, 1996; Groning, *Pharmazie* 51:337-341, 1996; Fotherby, *Contraception* 54:59-69, 1996; Johnson, *J. Pharm. Sci.* 84:1144-1146, 1995; Rohatagi, *Pharmazie* 50:610-613, 1995; Brophy, *Eur. J. Clin. Pharmacol.* 24:103-108, 1983; the latest Remington's, *supra*). For example, in one study, less than 0.5% of the daily dose of mifepristone was excreted in the urine; the drug bound extensively to circulating albumin (see Kawai, *supra*, 1989). The state of the art allows the clinician to determine the dosage regimen for each individual patient, GR antagonist and disease or condition treated. As an illustrative example, the guidelines provided below for mifepristone can be used as guidance to determine the dosage regiment, *i.e.*, dose schedule and dosage levels, of any GR antagonist administered when practicing the methods of the invention.

[0114] Single or multiple administrations of GR antagonist formulations can be administered depending on the dosage and frequency as required and tolerated by the patient. The formulations should provide a sufficient quantity of active agent, *e.g.*, mifepristone, to effectively inhibit or reverse the symptoms of depression induced by IL-2 medications. For example, a typical preferred pharmaceutical formulation for oral administration of mifepristone would be about 5 to 15 mg/kg of body weight per patient per day, more preferably between about 8 to about 12 mg/kg of body weight per patient per day, most preferably 10 mg/kg of body weight per patient per day, although dosages of between about 0.5 to about 25 mg/kg of body weight per day may be used in the practice of the invention. Lower dosages can be used, particularly when the drug is administered to an anatomically secluded site, such as the cerebral spinal fluid (CSF) space, in contrast to administration orally, into the blood stream, into a body cavity or into a lumen of an organ. Substantially higher dosages can be used in topical administration. Actual methods for preparing parenterally administrable GR antagonist formulations will be known or apparent to those skilled in the art and are described in more detail in such publications as Remington's, *supra*. See also Nieman, In "Receptor Mediated Antisteroid Action," Agarwal, *et al.*, eds., De Gruyter, New York, 1987.

EXAMPLES

[0115] The following examples are offered to illustrate, but not to limit the claimed invention.

Example 1: Use of mifepristone to ameliorate symptoms of depression in a patient undergoing IL-2 therapy

[0116] The following example demonstrates how to practice the methods of the invention.

Patient Selection

[0117] Individuals who are to begin or are currently undergoing IL-2 therapy. The patient typically has normal levels of cortisol for his or her age.

10 *Dosage Regimen and Administration of Mifepristone*

[0118] The glucocorticoid receptor (GR) antagonist, mifepristone, is used in this study. It is administered in dosages of 200 mg daily. Individuals will be given 200 mg of mifepristone daily for six months and evaluated as described below. Dosages will be adjusted if necessary and further evaluations will be performed periodically throughout treatment.

15 [0119] Mifepristone tablets are available from commercial sources such as Shanghai Hua Lian Pharmaceuticals Co., Ltd., Shanghai, China.

Assessing amelioration of symptoms of depression

[0120] To delineate and assess the effectiveness of mifepristone in ameliorating the symptoms of depression, a patient who is suffering from or is susceptible to depression associated with IL-2 therapy is examined, both before and after receiving mifepristone, for the presence and/or severity of depression symptoms. The detailed examination methods and criteria for assessing the condition of depression can be found in, *e.g.*, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV).

[0121] It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference in their entirety for all purposes.

WHAT IS CLAIMED IS:

- 1 1. A method for ameliorating the symptoms of depression in a patient
2 with normal levels of cortisol taking interleukin-2 (IL-2), comprising the step of
3 administering to the patient an effective amount of a specific glucocorticoid receptor
4 antagonist, with the proviso that the patient is not clinically depressed at the time IL-2
5 therapy is commenced, and is not otherwise in need of treatment with a glucocorticoid
6 receptor antagonist.
- 1 2. The method of claim 1, wherein the glucocorticoid receptor antagonist
2 is administered to the patient coextensively with IL-2.
- 1 3. The method of claim 2, wherein the glucocorticoid receptor antagonist
2 is administered to the patient during the entire time when the patient is taking IL-2.
- 1 4. The method of claim 1, wherein the glucocorticoid receptor antagonist
2 is administered to the patient taking IL-2 in conjunction with other treatment methods.
- 1 5. The method of claim 1, wherein the glucocorticoid receptor antagonist
2 is administered via intravaginal or intrarectal routes.
- 1 6. The method of claim 5, wherein the glucocorticoid receptor antagonist
2 is administered by suppositories.
- 1 7. The method of claim 1, wherein the glucocorticoid receptor antagonist
2 comprises a steroid compound.
- 1 8. The method of claim 7, wherein the glucocorticoid receptor antagonist
2 has a modified cortisol steroid backbone selected from the group consisting of removal of the
3 11- β -hydroxy group, aryl substitution of the 11- β -hydroxy group, 11- β -phenyl-
4 aminodimethyl steroids, 17- β -side chain modifications, alpha-keto-methane-sulfonate
5 derivatives of cortisol, and androgen type steroids.
- 1 9. The method of claim 7, wherein the glucocorticoid receptor antagonist
2 is selected from the group consisting of dexamethasone-oxetanone, 4-pregnene-11-beta,17-
3 alpha,21-triol-3,20-dione-21-methane-sulfonate, 16-methyl-9 alpha-fluoro-1,4-pregnadiene-
4 11 β ,17-alpha,21-triol-3,20-dione-21-methane-sulfonate, 11- β -(4-dimethyl-

5 aminoethoxyphenyl)-17- α -(propynyl)-17- β -hydroxy-4,9-estradien-3-one, and 17- β -
6 hydroxy-11- β -(4-dimethyl-aminophenyl)-17- α -(1-propynyl)estra-4,9-dien-3-one.

1 **10.** The method of claim 7, wherein the glucocorticoid receptor antagonist
2 is selected from the group consisting of (6 β ,11 β ,17 β)-11-(4-(dimethyl-amino)phenyl)-6-
3 methyl-4',5'-dihydro[estra-4,9-diene-17,2'(3H)-furan]-3-one, (11 β ,17 β)-11-(1,3-
4 benzodioxol-5-yl)-17-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one, (11 β ,17 α)-11-(4-
5 acetylphenyl)-17,23-epoxy-19,24-dinorchola-4,-9,20-trien-3-one, (7 β ,11 β ,17 β)-11-(4-
6 (dimethylamino)phenyl)-7-Me-4',5'-dihydrospiro(oestra-4,9-diene-17,2'(3H)-furan)-3-one]-,
7 (11 β , 17 α)-11,21-Bis[4-(dimethylamino)phenyl]-17-hydroxy-19-norpregna-4,9,dien-20-yn-
8 3-one, and (11 β ,17 α)-11-[4-(dimethylamino)phenyl]-17-hydroxy-21-[4-
9 (methylsulfonyl)phenyl]-19-norpregna-4,9-dien-20-yn-3-one

1 **11.** The method of claim 7, wherein the glucocorticoid receptor antagonist
2 comprises a steroidal skeleton with at least one phenyl-containing moiety in the 11- β
3 position of the steroidal skeleton.

1 **12.** The method of claim 11, wherein the phenyl-containing moiety in the
2 11- β position of the steroidal skeleton is a dimethylaminophenyl moiety.

1 **13.** The method of claim 12, wherein the glucocorticoid receptor
2 antagonist comprises mifepristone.

1 **14.** The method of claim 11, wherein the glucocorticoid receptor
2 antagonist is selected from the group consisting of RU009 and RU044.

1 **15.** The method of claim 1, wherein the glucocorticoid receptor antagonist
2 comprises a non-steroidal compound.

1 **16.** The method of claim 15, wherein the glucocorticoid receptor
2 antagonist comprises a modified pyrimidine compound

1 **17.** The method of claim 15, wherein the glucocorticoid receptor
2 antagonist is 4b(S)-benzyl-7(S)-hydroxy-7-(1-propynyl)-4b,5,6,7,8,8a(R),9,10-
3 octahydrophenanthrene-2-carboxylic acid (pyridine-4-ylmethyl)amide.

1 18. The method of claim 15, wherein the glucocorticoid receptor
2 antagonist is 4b(S)-benzyl-7(S)-hydroxy-7-(3,3,3-trifluoropropyl)-4b,5,6,7,8,8a(R),9,10-
3 octahydrophenanthrene-2-carboxylic acid (2-methylpyridin-3-ylmethyl)amide.

1 19. The method of claim 15, wherein the glucocorticoid receptor
2 antagonist is selected from the group consisting of 1-(o-chloro-alpha,alpha-
3 diphenylbenzyl)imidazole, N(triphenylmethyl)imidazole, N-([2-fluoro-9-
4 phenyl]fluorenyl)imidazole, N-([2-pyridyl]diphenylmethyl)imidazole, N-([4,4',4"]-
5 trichlorotrityl)imidazole, and N((2,6 dichloro-3-methylphenyl)diphenyl)methylimidazol

1 20. The method of claim 15, wherein the glucocorticoid receptor
2 antagonist is selected from the group consisting of 6-substituted-1,2-dihydro-N protected-
3 quinolines, octahydrophenanthrenyl carbamates, oxadiazolylalkoxyoctahydrophenanthrenes,
4 and octahydrophenanthrene hydrazines.

1 21. The method of claim 15, wherein the glucocorticoid receptor
2 antagonist is selected from the group consisting of octahydro-2-H-naphthol[1,2,-f]indole-4
3 carboxamide, cyclopent[f]indazole, and benz[f]indazole.

1 22. The method of claim 15, wherein the glucocorticoid receptor
2 antagonist is selected from the group consisting of 6H-dibenzo[b,d]pyran derivatives,
3 substituted aminobenzene derivatives, triphenylmethane derivatives, diphenyl ether
4 derivatives, and modified pyrimidine compounds.

1 23. The method of claim 15, wherein the glucocorticoid receptor
2 antagonist is selected from the group consisting of 1-(2-chlorotrityl)-2-methylimidazole, N-
3 (2-chlorotrityl)-L-prolinol acetate, 1-(2-chlorotrityl)-1,2,4-triazole, and 1-(2-chlorotrityl)-3,5-
4 dimethylpyrazole.

1 24. The method of claim 15, wherein the glucocorticoid receptor
2 antagonist is selected from the group consisting of cis-1-acetyl-4-(4-((2-(2,4-dichlorophenyl)-
3 2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl)methoxy)phenyl)piperazine, N-(2[4,4',4"-
4 trichlorotrityl]oxyethyl)morpholine, 1-(2[4,4',4"-trichlorotrityl]oxyethyl)-4(2-
5 hydroxyethyl)piperazine dimaleate, 4-(morpholinomethyl)-A-(2-pyridyl)benzhydrol, and 1,S-
6 bis(4,4',4"-trichlorotrityl)-1,2,4-triazole-3-thiol.

1 **25.** The method of claim 15, wherein the glucocorticoid receptor
2 antagonist is selected from the group consisting of 9-(3-mercapto-1,2,4 triazolyl)-9-phenyl-
3 2,7-difluorofluorenone, 5-(5-methoxy-2-(N-methylcarbamoyl)-phenyl)dibenzosuberol, 4a(S)-
4 benzyl-2(R)-chloroethynyl-1,2,3,4,4a,9,10,10a(R)-octahydro-phenanthrene-2,7-diol, and
5 4a(S)-benzyl-2(R)-prop-1-ynyl-1,2,3,4,4a,9,10,10a(R)-octahydro-phenanthrene-2,7-diol.

1 **26** The method of claim 15, wherein the glucocorticoid receptor
2 antagonist is an azadecalin compound.

1 **27.** The method of claim 15, wherein the glucocorticoid receptor
2 antagonist is a fused ring azadecalin compound.

1 **28.** The method of claim 1, wherein the glucocorticoid receptor antagonist
2 is administered once per day.

3 **29.** The method of claim 1, wherein the glucocorticoid receptor antagonist
4 is administered in an amount of between 0.5 mg and 20 mg per kg of body weight per day.

1 **30.** The method of claim 29, wherein the glucocorticoid receptor
2 antagonist is administered in an amount of between about 1 mg and 10 mg per kg of body
3 weight per day.

1 **31.** The method of claim 30, wherein the glucocorticoid receptor
2 antagonist is administered in an amount of between 1mg and 4 mg per kg of body weight per
3 day.

1 **32.** The method of claim 1, wherein the glucocorticoid receptor antagonist
2 is administered orally.

1 **33.** The method of claim 1, wherein the glucocorticoid receptor antagonist
2 is administered by a transdermal application, by a nebulized suspension, by an aerosol spray,
3 or by injection.